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Recent Advances in Antidepressant Drug Treatment

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Psychiatric research has made remarkable advances in understanding the pathophysiology of depressive illnesses. Biologic depressions are now understood as neurotransmitter deficiency diseases. Certain forms of depression are treated with tricyclic antidepressant drugs, which increase the amount of available neurotransmitters. Complicating the clinical picture, however, is the problem of wide variability of levels of tricyclic drugs in the plasma of persons receiving the same dosage. Another problem is the apparent linear dose-response relationship of imipramine hydrochloride and its sister compound desipramine hydrochloride while amitriptyline and nortriptyline follow an inverted U-shaped dose-response curve. However, with newer, more sophisticated diagnostic methods, combined with monitoring of tricyclic drug levels in plasma, therapeutic efficacy can approach 90 percent.

Available neurotransmitters also can be increased using monoamine oxidase (MAO) inhibitors. Although MAO inhibitors have been less popular than the tricyclic drugs, recent clinical research tends to support their efficacy. Distinct individual differences in the rate of metabolism of MAO inhibitors have been found. New methods are being devised to detect these differences and monitor directly the effects of these drugs. One of these methods, platelet MAO inhibition, shows some clinical promise.

Tricyclic drugs and MAO inhibitors have recently been joined by lithium carbonate, which shows notable efficacy in removing acute manic-depressive symptoms as well as preventing their return during maintenance treatment. Its utility in treating cyclic depressions without mania is now being explored by researchers.

TRICYCLIC ANTIDEPRESSANT drugs have been available for more than 20 years, but only relatively recently have they received widespread acceptance as clinically effective agents. Monoamine oxidase (MAO) inhibitor antidepressant drugs have been available somewhat longer but are still viewed as ineffective and potentially dangerous. It is not entirely clear why this has been so. Perhaps part of the explanation rests on the difficulties associated with making appropriate treatment-specific diagnoses. Not enough has been learned about the basic pathophysiology of the various depressive disorders. It is still debated, for ex-

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ABBREVIATIONS USED IN TEXT
ECT = electroconvulsive therapy
MAO = monoamine oxidase

ample, whether so-called neurotic depressive persons can be effectively treated with antidepressant drugs. However, fundamental gaps in our knowledge about the pharmacology of the antidepressant drugs have clearly been major stumbling blocks in their effective use. After arbitrarily choosing an antidepressant drug, physicians have been left with little more to guide their dosage regulation than their clinical experience. Unfortunately, often the only observable clue that a given drug is affecting the system has been the emergence of annoying side effects. More accurate information regarding tricyclic drug levels in blood is of utmost importance to clinicians. However, even today, few laboratories, outside research settings, can provide such information.

In contrast, a different course of events followed the introduction of lithium carbonate into the United States in 1971. From the diagnostic point of view, classic cases of mania present with readily diagnosable symptoms that sometimes literally scream out for treatment. The technical ease of monitoring levels of lithium carbonate in plasma has made it a very popular drug despite its fairly narrow therapeutic index.

This article reviews the clinically relevant literature concerning the tricyclic antidepressant drugs and the MAO inhibitors, with special emphasis on the newer methods of diagnosis and drug-level monitoring. Lithium carbonate and electroconvulsive therapy (ECT) also will be discussed as they relate to special types of depressions and drug treatment failures.

Theoretical Basis of Pharmacologic Action

The current etiologic theory of biologic depressions proposes a deficit of one or more central neurotransmitters. Originally labeled the catecholamine theory of depression, because of its focus on norepinephrine,[1,2] it now emphasizes the possible importance of low levels of other neurotransmitters such as the indolamine serotonin (5-hydroxytryptamine).[3-5] This theory points to deficient levels of serotonin as permitting the full manifestation of low norepinephrine levels in depression. Conversely, low serotonin, in the face of high norepinephrine, would express itself clinically as mania. This so-called permissive theory attempts to join unipolar depressions with bipolar (manic-depressive) depressions under a common biochemical defect. If correct, it might explain why manic-depressive patients in their depressed state are virtually indistinguishable from other depressive persons. The underpinnings of the neurotransmitter theories of depression rest on the observation that reserpine produces, in animals and man, psychomotor symptoms similar to those seen in clinical depression.[6] Examination of the brains of reserpinized animals shows a depletion of norepinephrine, serotonin and dopamine. Treatment with antidepressant drugs tends to restore these neurotransmitters to normal levels and removes the signs of psychomotor retardation.

Another, somewhat more dynamic theory suggests the existence of a critical balance of one or more neurotransmitter systems with acetylcholine. Just as the motor manifestations of parkinsonism are now seen as resulting from an imbalance of dopamine with respect to acetylcholine, depressive symptoms could be viewed as arising from lack of modulation of norepinephrine by acetylcholine.[7] Attempts to increase acetylcholine in manic patients by giving the cholinesterase inhibitor physostigmine have produced intriguing but inconsistent results. In some patients abrupt swings toward suicidal depression occurred, while in others there was only decreased motor activity.[8]

Tricyclic Antidepressant Drugs

Imipramine, the first tricyclic antidepressant drug, was discovered in the course of a search for a better chlorpromazine-like drug. While investigating the neuroleptic activity of imipramine, Kuhn[9] found that it was ineffective for the thought disorder of schizophrenics but produced improvement in depressed patients.

The commonly available tricyclic antidepressant drugs—imipramine, amitriptyline, desipramine, nortriptyline, protriptyline and doxepin—are structurally different from the phenothiazines only in apparently minor ways. For example, the sulfur atom in the phenothiazine molecule is replaced in the tricyclic drugs by a two-carbon or carbon-oxygen bridge. This similarity emphasizes the importance of minor structural changes in the production of critical differences in basic pharmacologic activity. The phenothiazines are thought to exert their antischizophrenic effect by dopamine-receptor blockade. The mechanism of action of the tricyclic drugs, as illustrated in Figure 1, is to increase the relative levels of neurotransmitter in

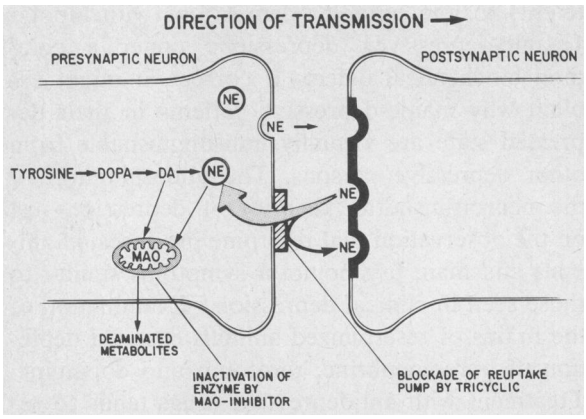

Figure 1.—Schematic representation of central norepinephrine (NE) nerve synapse. Note the pathways of neurotransmitter formation, release and reuptake. Partial inhibition of the reuptake pump by tricyclic antidepressant drug results in increased levels of transmitter capable of depolarizing the postsynaptic membrane. Inhibition of mitochondrial monoamine oxidase (MAO) leads to a build-up in precursors and stored neurotransmitter. (DA, dopamine.)

the synaptic cleft by blocking the presynaptic reuptake pump. Different tricyclic drugs vary in the degree to which they inhibit the reuptake of norepinephrine and serotonin. Desipramine acts almost exclusively on norepinephrine, while amitriptyline is most effective in blocking serotonin.[10]

Because tricyclic antidepressant drugs are quite lipid-soluble and therefore almost completely absorbed from the gastrointestinal tract, other routes of administration are unnecessary and are potentially hazardous. Once in the system, imipramine and amitriptyline are partially metabolized in the liver to their respective desmethyl derivatives—desipramine and nortriptyline. These active metabolites, in equilibrium with their parent compounds, undoubtedly contribute to the total antidepressant effect.

The pharmaceutical industry synthesized these derivatives in the hope that they might be found to exert their antidepressant action with a shorter lag period than their parent compounds. In numerous studies, however, no differences in onset of action or efficacy of any of the various tricyclic compounds have been found. One experimental tricyclic compound, amoxapine, does show a significantly shorter lag time but it apparently does not have increased overall efficacy when compared with standard tricyclic drugs.[11]

Clinical Effects

In nondepressed persons, tricyclic drugs produce varying degrees of sedation. In depressed patients, however, they produce striking improvement in negativistic ruminations, depressed mood and slowed motor behavior—generally with noticeable changes three to ten days after commencing treatment. These drugs cannot be termed psychostimulants, because they produce a normal mood rather than euphoria or hyperactivity. Controlled studies indicate that at least 70 percent of depressed patients are substantially benefited by tricyclic antidepressant drugs, while only 40 percent are helped by a placebo in the same period.[12]

Apparently there are populations of responders and nonresponders to the tricyclic antidepressant drugs (as well as to MAO inhibitors); therefore, the pretreatment determination of potential response to the available types of treatment is of great importance. Surprisingly few studies have claimed to identify variables associated with good drug response or subpopulations of depressed patients who are susceptible to specific types of antidepressant drugs. However, Pare and associates[13] argued that when a genetic relative of a patient has responded well to either MAO inhibitors or tricyclic medications, the patient may be expected to respond to the same class of medication or to a specific drug within a class. For example, it is not uncommon in clinical practice to find a patient who responds only to a specific tricyclic drug. There is often a good chance of finding other affected members of his family who have responded to the same drug. Consequently, valuable information regarding a patient's treatment can be uncovered by taking a careful family history.

Kiloh and associates[14] found that predictors of a positive response to imipramine are associated with more severe endogenous depressions. These endogenous or biologic symptoms typically present as early morning wakening, psychomotor retardation or agitation, weight loss, and overwhelming feelings of worthlessness and guilt. However, there tends to be a less favorable response to imipramine by patients with neurotic and characterological depressions whose premorbid personalities have included hypochondriacal, self-pitying and hysterical traits. Delusional patients, according to Horden and associates,[15] tend to have a poor response to imipramine. Glassman and coworkers[16] found that by excluding delusional depressive patients, the response rate with imipramine approached 85 percent. Good diagnosis, based on readily recordable signs and

symptoms, is becoming even more essential for definitive treatment.

Some investigators[17,18] have claimed that those depressed patients who show a transient elevation of mood when amphetamine is given, tend to respond better to imipramine than to amitriptyline. This encouraging finding should be carefully investigated since this simple pretreatment test could conceivably point the way toward placing the patient on the optimal drug and obviating the need to switch drugs during treatment.

Dosage

As has been stated above, dosage is increasingly recognized as an important factor in the drug treatment of depression. Many of the studies that have shown poor results with antidepressant drugs undoubtedly reflect the results of inadequate doses—either subtherapeutic amounts or too short a trial. Only after three to four weeks at adequate dosage can one be sure that unresponsive patients will not improve on a particular drug. Simply increasing the dosage may not be the final answer, however, as will be discussed in the next section on blood levels. Many psychiatrists favor dose levels of 150 mg to 250 mg per day of imipramine or amitriptyline—a level that should be achieved over a period of several days to a week. In contrast, other investigators feel that the ideal therapeutic dose lies between 50 mg and 600 mg per day.[19] Protriptyline seems to be an exception. It is more potent than the other tricyclic antidepressant drugs, and smaller daily doses of this drug are required. A study of protriptyline hydrochloride levels in blood indicated that the greater relative potency may be due to slower metabolism of the drug, since circulating levels are in the same range as those of other tricyclic antidepressant drugs.[20] Flexible dosage, within boundaries defined by known properties of the particular drug, will doubtless increase the response rate.

Blood Levels

Approximately 30 percent of depressed patients do not initially respond to tricyclic medication. Some of these patients appear to suffer from forms of depression that are not affected by tricyclic antidepressant drugs. Others do not respond because levels of the medication in the blood are either too low or too high for good therapeutic effect. This is due presumably to variations in the rate of metabolism.

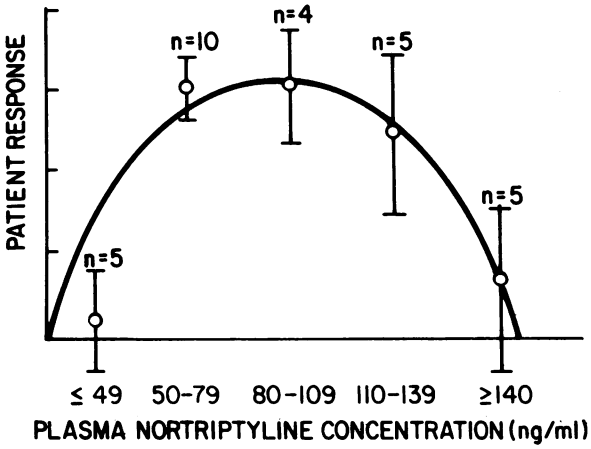

Figure 2.—Relationship between antidepressant response and steady-state plasma concentrations in 39 patients receiving 25 to 75 mg nortriptyline hydrochloride three times a day. Maximum benefit was found in the range of 50 to 139 ng per ml (adapted from Asberg et al[24]).

There are pronounced individual differences in levels of tricyclic drugs in plasma among patients given the same dosage—up to 40-fold in one study.[21] Once a maintenance dose is started, drug levels in the blood tend to build up over the course of a week until they reach equilibrium. However, some patients for various reasons have reduced metabolism or diminished blood and tissue binding capacity; normal doses of medication for these patients rapidly produce toxicity.

In other patients normal doses are metabolized so rapidly that effective tricyclic drug levels fail to develop in blood and brain. Studies of close relatives of patients in whom the drugs are metabolized either rapidly or slowly have shown that they also have unusual rates of drug metabolism.[22] Therefore, genetics plays an important role in this particular effect.

Rapid metabolism of tricyclic drugs may also result from simultaneous administration of drugs that cause induction of hepatic enzymes. It has been shown, for example, that phenobarbital reduces the levels of tricyclic drugs in plasma by approximately 50 percent.[23]

In studies by Asberg and associates[24] and Kragh-Sorensen and associates[25] the relationship between concentrations of nortriptyline in plasma and therapeutic response was carefully documented. As can be seen in Figure 2, among patients who failed to respond, there were those with very high and very low blood levels of nortriptyline. Reduction of dose for nonresponding patients with abnormally high concentrations, while in-

creasing the dose in patients with low levels, resulted in rapid response for a significant number of these subjects. It has been suggested that at abnormally high levels of nortriptyline, some paradoxical pharmacologic property supervenes to nullify the principal effect of the drug. The term therapeutic window has been coined to describe this inverted U-shaped dose-response curve.[26]

Braithwaite and associates[27] produced similar findings in their studies of levels of amitriptyline in plasma. Low plasma levels of both amitriptyline and nortriptyline were found to be ineffective, whereas moderate levels produced good therapeutic results. Gruvstad[28] reanalyzed these data and found a tendency for patients with elevated blood levels to have a poorer response than patients with intermediate levels. Some controversy, however, has arisen with the failure of other research groups to confirm these findings.[29,30]

Although the weight of evidence supports the concept of a therapeutic window for nortriptyline and possibly amitriptyline this may not be the case for imipramine. Glassman and associates[16] found that this tricyclic compound follows a more linear plasma-response relationship. This can be seen in Figure 3, which reports the correlation of imipramine (together with its active metabolite desipramine) with patient response.

In summary, preliminary clinical findings indicate that there can be pronounced individual differences in response to the various tricyclic antidepressant drugs. Response also appears to be a function of the concentration in the plasma of a given drug; nonresponse, in many cases, indicates overly high concentrations as well as inadequate concentrations. Adjustments of medications to achieve therapeutic blood levels currently must be based on clinical acumen until routine and readily available laboratory procedures are developed to accomplish the same results.

Maintenance Treatment to Prevent Recurrent Depression

It has been estimated that of persons who experience an acute depression nearly half will have a recurrence at some time in their lives. This relapse rate becomes much more frequent in some patients. For example, in a survey of nine controlled studies that examined the relapse rate of patients with recurrent depression during the first year of untreated follow-up, Kessler[31] reported a range of 36 percent to 91 percent with

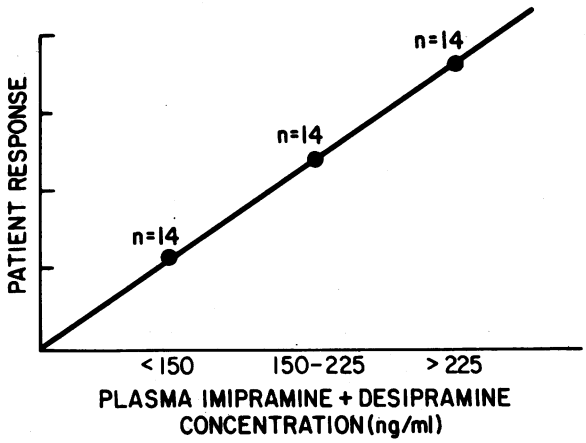

Figure 3.—Linear relationship of plasma level to antidepressant response in 42 patients receiving 100 to 300 mg of imipramine hydrochoride a day. Note that the combined plasma levels of imipramine hydrochloride and its desmethyl derivative, desipramine hydrochloride, are reported. The higher the plasma level of imipramine hydrochloride and desipramine hydrochloride the greater the fequency of response (adapted from Glassman et al[16]).

a mean of 64 percent. For many patients, then, maintenance treatment to prevent relapse gains central importance in therapy.

Recently, there have been three large collaborative studies concerning the role of maintenance therapy for patients initially treated with tricyclic drugs. Klerman and associates[32] studied 150 moderately ill depressive women, comparing the relative efficacy of maintenance on amitriptyline, individual psychotherapy and combination treatment. A no-pill, low-contact control group was included as well. At eight months, 36 percent of the control group, who received no treatment, had relapsed, while 12 percent of the drug therapy group and 16 percent of the psychotherapy group had relapsed. Relapses for the group who received combined drug therapy and psychotherapy did not differ significantly from those for groups on either drug therapy alone or psychotherapy alone.

A similar collaborative study was conducted by Mindham and associates[33,34] in Great Britain. After recovery, patients who were initially treated with tricyclic drugs were assigned randomly to either maintenance treatment (a reduced dosage of the tricyclic drug each had responded to) or placebo. A substantial prophylactic effect of the tricyclic drugs was shown. At the end of six months, approximately 50 percent of patients on placebo had relapsed compared with a relapse rate of 22 percent for patients on active medica-

tion. In a Veterans Administration collaborative study, Prien and associates[35] also compared imipramine with placebo and found that imipramine had significant prophylactic properties. In these severely ill patients in hospital, 92 percent relapsed on placebo compared with 48 percent who relapsed on drug treatment.

Davis[36] recommended maintaining the recovered patient for at least one month at full dosage before attempting a gradual stepwise reduction. Presumably those who relapse will do so less abruptly and can then be stabilized at a slightly higher dosage. Kragh-Sorensen and associates,[37] however, cautioned against arbitrary reduction in dosage from the level that was found to be effective in treating the acute episode. They pointed out that tricyclic drug levels are in stable equilibrium over time—neither inducing their own metabolism necessitating dosage increases nor accumulating in the body with adverse effects. Paykel and associates[38] found distinct advantage in maintaining patients on amitriptyline hydrochloride for eight months as compared with two months.

Clearly, some patients will never experience a recurrence of the original depression while others are in perpetual cycle of recurrent depression. Since there are no accurate predictors of relapse in the individual patient, except what is gathered from history, it is probably wise to treat most first-time depressions with maintenance medication for several months at a reduced dosage and most relapsing depressions with much longer stabilization at higher dosage.

For those patients who do not respond to tricyclic drugs or MAO inhibitors, or for those who are medically unsuitable for drug treatment, electroconvulsive therapy (ECT) is offered as an alternative. In a recent review of the efficacy of ECT, Davis and Ericksen[39] found an unusually high relapse rate in several studies. The rate was highest within the first few months after completion of treatment.

Two different investigations have sought to determine whether post-ECT relapse could be prevented by maintenance treatment with tricyclic drugs. Seager and Bird[40] employed a random assignment, double-blind design and followed post-ECT patients who received either placebo or imipramine for six months or until relapse occurred. The maintenance tricyclic medication had an impressive prophylactic effect: Of the group on imipramine maintenance, only 17 percent relapsed, whereas relapses occurred in 69 percent of the patients who received placebos. Following a similar design (post-ECT patients randomly assigned to receive amitriptyline or diazepam), Kay and associates[41] found that relapses occurred in a greater proportion of patients receiving diazepam than in the group receiving amitriptyline. Though neither of these studies of post-ECT patients involved large samples, the results were consistent in showing prophylactic properties for the tricyclic drugs. Because patients who are treated with ECT tend to be more profoundly depressed than others who receive drug therapy, they probably have a greater inherent tendency to relapse—and to relapse to the same level. It is therefore recommended that, whenever possible, ECT-treated patients should be given maintenance treatment with tricyclic drugs.

Treatment Combinations

Although not generally recommended in the literature, tricyclic antidepressant drugs can be safely combined with MAO inhibitors.[42,43] Whether this leads to enhanced efficacy is debatable, although most psychiatrists have had the experience of treating or seeing patients in whom remissions were achieved only with this combination.

Some interesting studies have shown an enhanced therapeutic response to the combination of imipramine hydrochloride with triiodothyronine. This effect is seen only in depressed women and not in men.[44] It also has been found that triiodothyronine alone has antidepressant properties, as does thyrotropin-releasing hormone.[45]

There is a loosely defined subpopulation of severely depressed patients who may benefit from a combination of antischizophrenic and antidepressant drugs. In my experience, family histories of these actively hallucinating persons occasionally include manic-depressive illness in close relatives; and such patients can benefit from treatment with lithium carbonate. If this fails, ECT is usually exceedingly beneficial and can be lifesaving in suicidal or very debilitated patients.

A common experience in evaluating patients who are unresponsive to treatment is the discovery that multiple drugs in irrational combinations have been administered, producing a toxic-confusional state or an atropine psychosis. Polypharmacy should be avoided if at all possible. Depressions tend to be time-limited, and medica-

tion side effects in many cases only complicate and prolong the natural course of the illness.

Lithium Carbonate

Lithium carbonate has gained a solid reputation in the treatment of bipolar manic-depressive illness. It is useful in the acute manic attack as well as in maintenance treatment to prevent further cyclic disturbances.[46,47] Moreover, some patients receiving maintenance treatment with lithium carbonate appear to benefit from a mild antidepressant action of the drug. These various effects naturally raise questions of whether lithium carbonate might be useful in treating other types of depression.

Unfortunately, lithium carbonate has been found to be a poor antidepressant medication in typical unipolar depression. Under active investigation, however, is its possible use in the prophylaxis of recurrent depression. A large collaborative study,[36] which examined this issue, showed that lithium carbonate has a somewhat limited effect in preventing further depressions; in nearly half of the patients relapse occurred within two years. In a recent follow-up of the original report, Prien and Caffey[48] suggested that higher levels of lithium in the serum produced acceptable prophylaxis. Patients with serum levels between 0.8 and 1.0 mEq per liter were as free from relapse as were those patients receiving imipramine in doses of 75 mg to 125 mg per day. However, patients with levels of 0.7 mEq per liter or less relapsed as frequently as did those patients receiving placebo. Because lithium carbonate typically must be taken several times a day and tricyclic drugs need to be taken only once a day, it might be difficult to convince patients to try maintenance with lithium carbonate without more specific indications. More research is needed in this area as well as in the area of the safety of lithium carbonate for long-term maintenance treatment. A disturbing report of possible nephrotoxicity involving lithium carbonate has caused many physicians to consider more carefully the reasons for prescribing this drug.[49]

Monoamine Oxidase Inhibitors

The first drugs with sustained antidepressant activity to be discovered were the monoamine oxidase (MAO) inhibitors. Although infrequently used today in general psychiatric practice, they are beginning to be reexamined for their possible therapeutic role in special clinical problems.

Iproniazid, the first MAO inhibitor, was originally used in the treatment of tuberculosis. Observers noted that in some of these patients iproniazid produced euphoria and mood elevation. Shortly afterward it was found that administration of this drug to more typical depressed patients produced favorable antidepressant results. Zeller and associates[50] established that the probable mechanism of action lay in the inhibition of the enzyme monoamine oxidase, resulting in an increase of neurotransmitters.

Monoamine oxidase is a ubiquitous enzyme that deaminates endogenously produced monoamines and monoamine-like substances acquired through food or drugs. In the central nervous system this mechanism helps to dispose of excess neurotransmitters. These neuronal monoamines (catecholamines and indolamines) are deaminated either before release or after reuptake by intraneuronal MAO located on the mitochondrial membrane, as shown in Figure 1.

Two classes of MAO inhibitors are in current use: the hydrazines and the nonhydrazines. The hydrazines (represented by phenelzine, nialamide and isocarboxazid) are structurally similar to iproniazid. They cause an irreversible inhibition; that is, new monoamine oxidase enzyme must be produced to restore the capacity to deaminate. Tranylcypromine is the only nonhydrazine MAO available at present for clinical use. It is similar to amphetamine in its structure and may produce some of its antidepressant effects by means of an amphetamine-like mechanism.[51]

Efficacy

Although MAO inhibitors have been available longer than tricyclic drugs, their efficacy is still questioned. A number of MAO inhibitors have been introduced and later withdrawn. Hepatotoxicity associated with iproniazid necessitated its early withdrawal, while other MAO inhibitors have been supplanted by newer agents because of lack of evidence that they were effective.

A growing body of literature shows that at least one MAO inhibitor, phenelzine, is effective. It is the only MAO inhibitor rated effective by the Food and Drug Administration. In their review of the efficacy studies, Robinson and associates[52] pointed to inadequate dosage as a principal reason for poor results with phenelzine. In their own double-blind study comparing phenelzine in a dosage of 60 mg per day with amitriptyline in a dosage of 75 mg per day there was rapid and

nearly identical improvement in both groups. This is the best evidence that an MAO inhibitor might be as effective as a tricyclic antidepressant drug.

Tranylcypromine is classified as an MAO inhibitor, although the appropriateness of this classification is in some doubt. In addition to MAO-inhibiting action, this agent may share some pharmacologic characteristics of the tricyclic drugs and amphetamines; that is, reuptake inhibition and direct agonist effects, respectively. Although tranylcypromine appears to be effective, studies have not been sufficient to permit a definitive statement.[53]

Evidence from double-blind studies leaves some doubt about the efficacy of isocarboxazid and nialamide. Negative results of these studies may derive from methodological insufficiencies, for example, underdosage or choice of inappropriate experimental population; however, the trend of the findings clearly raises questions about the effectiveness of these drugs.

Treatment of Atypical Depression With MAO Inhibitors

A number of reports suggest that MAO inhibitors may preferentially improve depressions with anxiety, phobic or other atypical features. In an early retrospective study of iproniazid, Alexander and Berkely[54] reported that neurotically depressed patients responded better (65 percent of 25 cases) than psychotic depressive patients (28 percent of 25 cases). Patients classified as having psychasthenic-anhedonic reaction responded fairly well (38 percent of 16 cases), while typical depressive patients responded poorly (26 percent of 38 cases). The most frequent complaints of patients who eventually responded were inability to work, fatigue, exhaustion, listlessness, not feeling well, unhappiness, being "down," inability to eat, diffidence and lack of self-confidence.

West and Dally[55] analyzed the symptoms of 101 depressed patients who were treated with iproniazid. A special group of atypical or hysterical depressive patients had the most rapid and unexpected responses. This form of depression was seen as a chronic condition with a high frequency of symptoms of fatigue, phobic anxiety and somatic complaints. Conversely, these depressions were not associated with classic endogenous symptoms such as early wakening, anorexia with weight loss, self-reproach and diurnal fluctuation in symptoms.

Robinson and associates[56] assessed the effects of phenelzine and placebo in a group of 88 outpatients with the diagnosis of depressive anxiety state. In contrast to the group receiving placebos, in the group receiving phenelzine there was significant improvement, which was most pronounced on dimensions of hypochondriasis, agitation, irritability and psychomotor change.

These studies suggest that MAO inhibitors may have special efficacy in those depressed patients who are often classified as neurotic. In these patients the most common symptom, besides depression, seems to be a great deal of somatization.

Treatment of Phobic Anxiety With MAO Inhibitors

In addition to their antidepressant effects, MAO inhibitors have been found effective in the treatment of phobic anxiety, as have the tricyclic antidepressant drugs. Kline[57] reported initial success with MAO inhibitors in cases of phobic-anxiety. Subsequently, Tyrer and associates[58] reported systematic, well-controlled studies in which phenelzine was significantly more effective than placebo in treating phobic-anxiety. Improvement often took up to two months to become manifiest. Consequently, these authors suggested that treatment regimens should allow for continuous treatment over a minimum of two months. The successful treatment of an individual phobic patient is illustrated in Figure 4. Details of this treatment will be discussed in the following section.

Biochemical Correlates of Effectiveness

MAO inhibitors affect the monoamine oxidase system throughout the body as well as in the central nervous system. There is the theoretical possibility that peripheral measurements of the inhibition of this enzyme could provide an indicator of central effectiveness. There are several reasons why this line of investigation might prove fruitful.

All persons seem to fall into one or the other of two genetically distinct groups according to the rate at which they metabolize certain drugs by acetylation. There are fast acetylators and slow acetylators. Since hydrazine MAO inhibitors are metabolized by acetylation, there is a distinct possibility that because of different acetylation rates some patients develop plasma levels of drug either too low or too high to be effective.[59] Nontherapeutic levels in plasma could develop even though patients were taking oral doses well within the recommended range.

Several investigative groups have measured

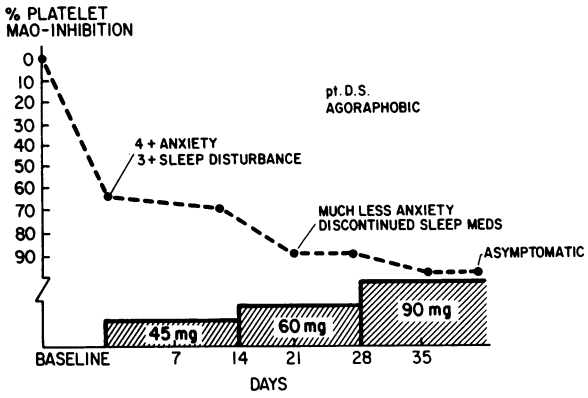

Figure 4.—Monoamine oxidase (MAO) inhibition as measured by percentage of platelet MAO inhibition in an agoraphobic patient receiving increasing doses of phenelzine sulfate. The patient showed improvement at 85 percent but at 90 percent cleared completely.

peripheral MAO inhibition in platelets from patients on phenelzine as an indirect measure of central MAO inhibition. Robinson and associates[60] reported a 68 percent improvement in depressed patients reaching 90 percent inhibition with phenelzine, whereas only 40 percent of patients improved at less than 90 percent inhibition. These authors suggested that an inhibition threshold may have to be exceeded before therapeutic benefit can be expected.

Figure 4 shows an example from a research study using an agoraphobic patient from the author's practice. Along the abscissa are graphed the oral dosages of phenelzine prescribed during treatment. The ordinate shows the percentages of MAO inhibition as measured from his platelets. This patient probably was a rapid acetylator; he did not obtain adequate MAO inhibition, and hence complete response, until the dose was pushed to a relatively high level.

Side Effects

The MAO inhibitors have a reputation for causing potentially dangerous hypertensive crises in the presence of sympathomimetic drugs or foods that contain tyramine. This reputation undoubtedly contributes to clinicians' lack of enthusiasm for MAO inhibitors. In actual practice, however, hypotension is a more frequent problem than hypertension. This is especially true at the start of treatment even with low dosage.

Patients taking MAO inhibitors should be carefully instructed to abstain from the following foods: pickled herring; chicken livers; wine, beer and sherry; aged cheeses, and the pods of broad beans.[61] Other foods that can be potentially interactive include figs, raisins, soy sauce, sour cream, bananas, sausages and coffee. Flushing of the skin and a mild headache are the most common reactions following consumption of one of the above foods. Many patients, however, are able to eat many of these foods without experiencing any side effects. Nevertheless, the strictest warnings must be given regarding the use of sympathomimetic medications and levodopa.

Another troublesome side effect that develops in many patients is the accumulation of interstitial fluid. This can be found in the form of dependent edema but also may be seen localized to one hand, or the face, if it has received recent trauma. The cause is not known but probably relates to subtle autonomic dysfunction in the peripheral circulation and should be viewed as an indication to lower the dosage.

Conclusions

- Research findings indicate that the efficacy of tricyclic antidepressant drugs can be increased by more accurate diagnosis and monitoring of treatment response. Determination of plasma levels eventually will give clinicians the needed information to adjust dosage for optimal response, but until that time, flexibility of dosage seems to be the best approach.
- Lithium carbonate shows unique properties in the treatment of bipolar (manic-depressive) patients. It may have a prophylactic effect in recurrent unipolar depressive disease as well, especially at higher plasma levels.
- Electroconvulsive therapy, long a mainstay of antidepressant treatment, is now most effectively utilized in the special cases of drug treatment failure. Maintenance treatment with tricyclic drugs for the post-ECT patient is the most rational approach to avoid relapse.
- As the efficacy of MAO inhibitors has been called into question, new evidence has emerged to support their usefulness. Better measures of adequate enzyme inhibition have shown that dosage has often been inadequate because of rapid acetylation in some patients.

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